(57) (Abstract)

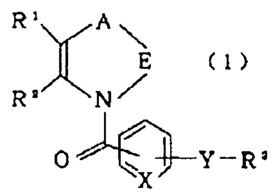
Object

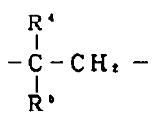
To put forward a novel compound having vasopressin antagonism, useful as therapy and/or preventative agent for hypertension, cardiac failure, renal failure, edema or the like.

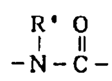
Construction

A compound represented by formula (1) and salts thereof

[wherein, R1 and R2 together with adjacent C atoms form benzene ring, pyridine ring or thiophene ring, R3 is (i) lower alkenyl which may be substituted, (ii) aryl or (iii) heterocyclic group which may be substituted, A denotes formula (2) (wherein, (i) R4 and R5 are H, (ii) R4 is H and R5 is –OH or lower alkylamino, or (iii) R4 and R5 are oxo), E is lower alkylene or phenylene, X is CH or N, and Y is a single bond or formula (3) (wherein R6 is H, tolyl benzoyl or the amino which may be substituted)].


(1)

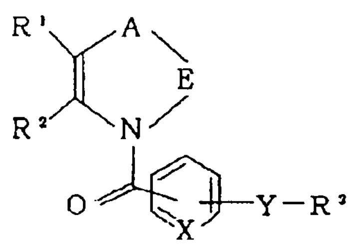

(2)


(3)

Patent Claim

Claim 1

A benzamide compound represent by general formula (I) and salts thereof


(I)

[wherein, R1 and R2 together with adjacent carbon atoms form benzene ring, pyridine ring or thiophene ring, and those rings may be substituted by lower alkyl, R3 is (i) the lower alkenyl which may be substituted by the substituent selected from the group

comprising cyano and aryl, (ii) aryl or (iii) the heterocyclic group which may be substituted by the substituent selected from the group comprising lower alkyl and aryl, A is

$$\begin{array}{c} R^4 \\ | \\ -C-CH_2- \\ | \\ R^5 \end{array}$$

(wherein, (i) R4 and R5 are each hydrogens, (ii) R4 is a hydrogen and R5 is hydroxy or lower alkyl amino, or (iii) R4 and R5 link together to form oxo), E is lower alkylene or phenylene, X is CH or N, and Y is a single bond or

$$\begin{array}{cc} R^6 & O \\ | & \| \\ -N- & C- \end{array}$$

(wherein, R6 is (i) hydrogen, (ii) tolyl benzoyl or (iii) the amino which may be substituted by lower alkyl or acyl). Wherein, when Y is a single bond or

$$\begin{array}{c} O \\ \| \\ -NH-C- \end{array}$$

then 1) R1 and R2 together with adjacent carbon atoms form pyridine ring or thiophene ring, and those rings may be substituted by lower alkyl, or
2) R3 is a lower alkenyl which may be substituted by the substituent selected from the group comprising cyano and aryl or heterocyclic group substituted by the substituent selected from the group comprising lower alkyl and the aryl, or
3) E is a phenylene].

Detailed Description of the Invention

(0001)

Sphere of Application in Industry

This invention relates to a novel benzamide compound and salts thereof. More particularly, this invention relates to a novel benzamide compound and salts thereof useful as drug, having activities such as vasopressin antagonism, vasodilator action, antihypertensive action, action of inhibiting release of carbohydrate from liver, mesangial cell proliferation inhibitory action, diuresis action, platelet aggregation inhibitory action, oxytocin antagonism or the like.

(0002)

Technology of the Prior Art

As compounds having vasopressin antagonism, for example compounds described in International Patent Application WO94/14796 and Kokai 6-172317 are known.

(0003)

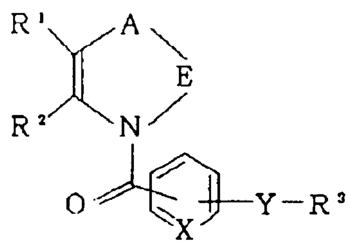
Object of the Invention

The object of this invention is to put forward a novel benzamide compound and salts thereof having the aforesaid activity and which is useful.

(0004)

The benzamide compound comprising the object of this invention is a novel compound and is represented by general formula (I)

(0005)

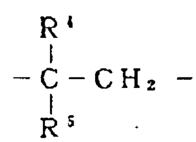


(I)

(0006)

[wherein, R1 and R2 together with adjacent carbon atoms form benzene ring, pyridine ring or thiophene, and those rings may be substituted by lower alkyl, R3 is (i) lower alkenyl which may be substituted by substituent selected from the group comprising cyano and aryl, (ii) aryl or (iii) heterocyclic group which may be substituted by substituent selected from the group comprising lower alkyl and aryl, A is

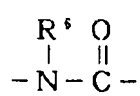
(0007)



(0008)

(wherein, (i) R4 and R5 are each hydrogens, (ii) R4 is hydrogen and R5 is hydroxy or lower alkyl amino, or (iii) R4 and R5 link together to form oxo), E is lower alkylene or phenylene, X is CH or N, and Y is a single bond or

(0009)



(0010)

(wherein, R6 is (i) hydrogen, (ii) tolyl benzoyl or (iii) the amino which may be substituted by lower alkyl or acyl). Wherein, when Y is a single bond or

(0011)

$$-NH-\overset{\displaystyle O}{\overset{\|}{C}}-$$

(0012)

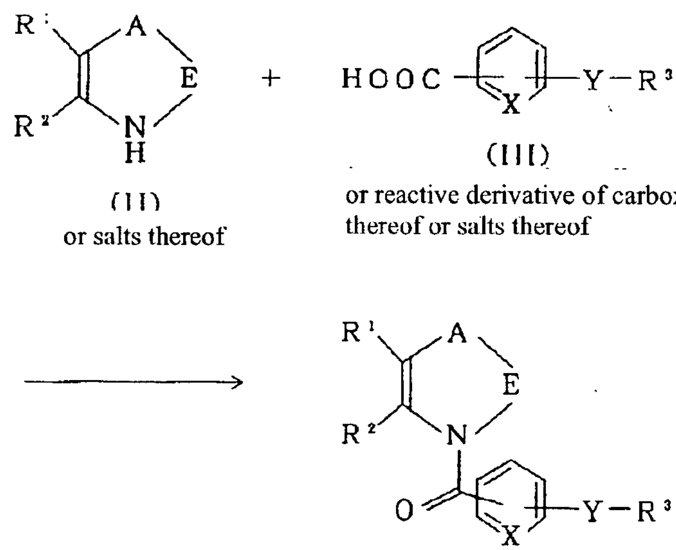
then 1) R1 and R2 form pyridine ring or thiophene ring together with adjacent nitrogen atom, and those rings may be substituted by lower alkyl, or
2) R3 is a lower alkenyl which may be substituted by the substituent selected from the group comprising cyano and aryl or heterocyclic group substituted by the substituent selected from the group comprising lower alkyl and the aryl, or
3) E is a phenylene].

(0013)

Target compound (I) or salts thereof can be produced by various processes represented by following reaction equations.

(0014)

Process 1



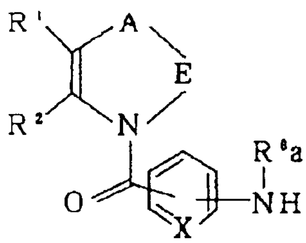
(II)
or salts thereof

(III)
or reactive derivative of carboxy-group thereof or salts thereof

(I)
or salts thereof

(0015)

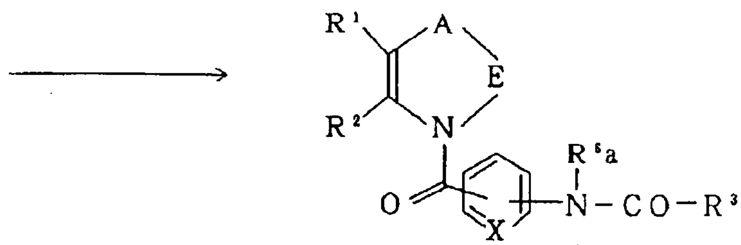
Process 2



(IV)
or salts thereof

+ HOOC−R³

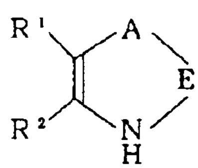
(V)
or reactive derivative of carboxy-group thereof or salts thereof



(Ia)
or salts thereof

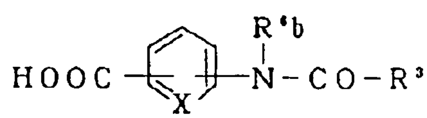
(0016)

Process 3

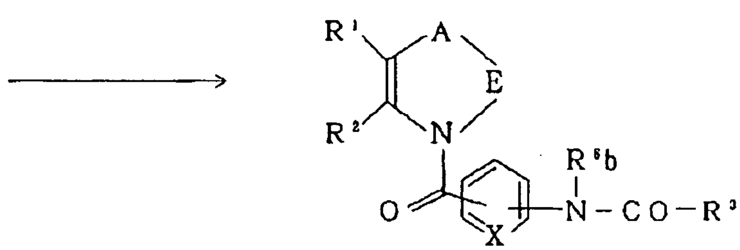


(II)
or salts thereof

+



(IIIa)
or reactive derivative of carboxy-group thereof or salts thereof

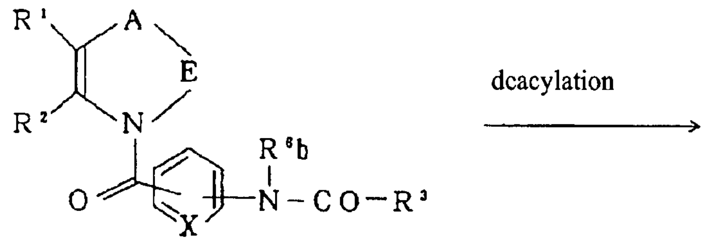


(Ib)

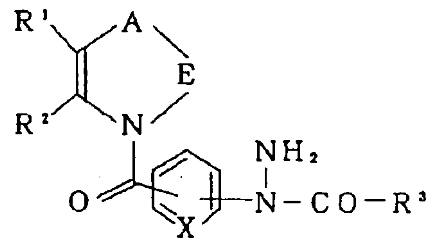
or salts thereof

(0017)

Process 4



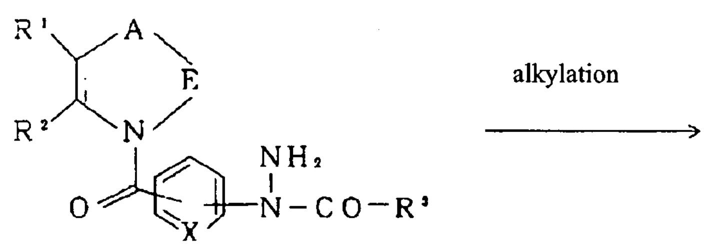
(Ib)
or salts thereof



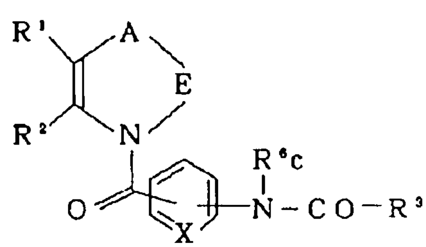
(Ic)
or salts thereof

(0018)

Process 5



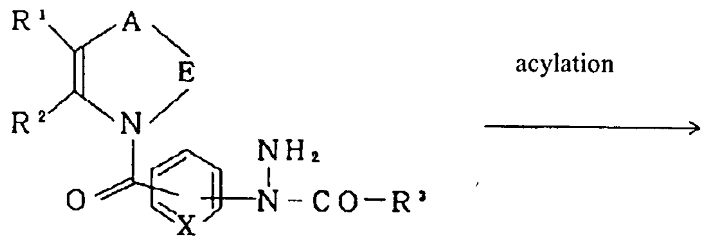
(Ic)
or salts thereof



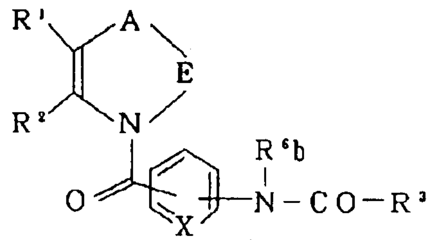
(Id)
or salts thereof

(0019)

Process 6



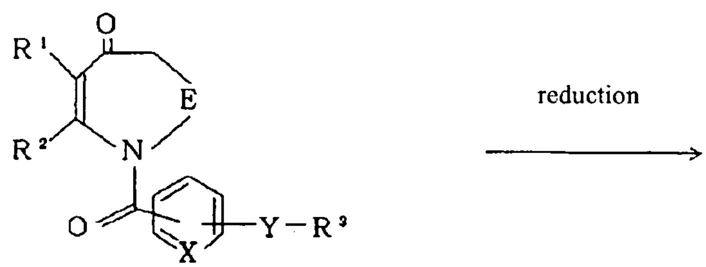
(Ic)
or salts thereof



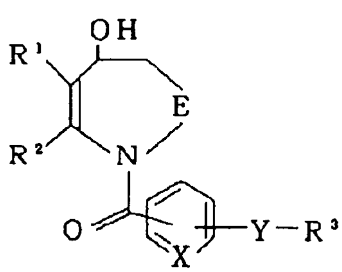
(Ib)
or salts thereof

(0020)

Process 7



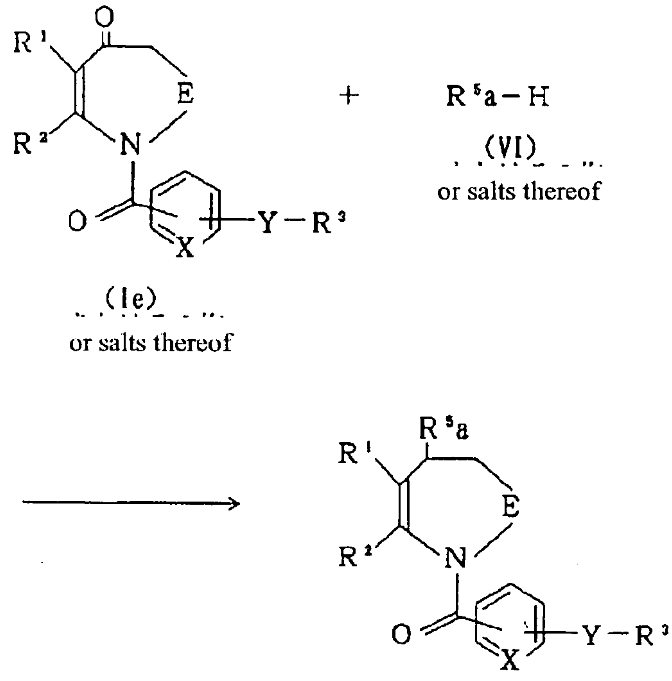
(Ie)
or salts thereof



(If)
or salts thereof

(0021)

Process 8



(Ie)
or salts thereof

(VI)
or salts thereof

(Ig)
or salts thereof

(0022)

In the aforesaid reaction equations, R1, R2, R3, A, E, X and Y have the same definition described above respectively. R6a is hydrogen or tolyl benzoyl, R6b is acylamino, R6c is lower alkyl amino, and R5a is lower alkyl amino.

(0023)

In the aforesaid and subsequent explanation of this specification, ideal examples of various kinds of definition including the range of this invention are described in greater details below. The term "lower" denotes group having 1-6 carbon atoms and preferably group having 1-4 carbon atoms unless otherwise particularly stated. Suitable "lower alkyl" and suitable lower alkyl moiety in the representations of "heterocyclic lower alkyl", "lower alkyl sulfonyl", "lower alkyl amino lower alkyl", "lower alkyl carbamoyl", "acyl lower alkyl", "lower alkyl amino" and "aryl lower alkyl" may be straight or branched chain form such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, hexyl or the like, and among them, 1-4C alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl or the like is preferred.

(0024)

As suitable "aryl" and suitable aryl moiety in the representation of "aryl sulfonyl", 6-10C aryl such as phenyl, naphthyl, lower alkyl substituted phenyl (for example tolyl, xylyl, mesityl, cumenyl, ditertiary butyl phenyl and the like) or the like isproposed. In particular phenyl, tolyl or xylyl is preferred.

(0025)

As ideal "halogen", fluorine, chlorine, bromine and iodine are proposed. In particular fluorine, chlorine is preferred.

(0026)

As ideal "lower alkyl amino", mono- or di- lower alkyl amino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, tertiary butyl amino, isobutyl amino, pentyl amino, hexyl amino, dimethylamino, diethylamino, dipropylamino, dibutyl amino, diisopropylamino, dipentyl amino, dihexyl amino, N-methylethylamino or the like are proposed. Particularly preferable is methylamino, dimethylamino.

(0027)

As suitable "heterocyclic group" and suitable heterocyclic moiety in the representations of "heterocyclic lower alkyl" and "heterocyclic carbonyl", a group containing at least 1 heteroatom selected among nitrogen atom, sulfur atom and oxygen atom is good, and includes saturated or unsaturated monocyclic or polycyclic heterocyclic group. As preferred heterocyclic group, 3-6 membered unsaturated heteromonocyclic group containing 1-4 nitrogen atoms, for example pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl [for example, 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl and the like], tetrazolyl [for example, 1H-tetrazolyl, 2H-tetrazolyl and the like) or the like; 3-7 membered saturated heteromonocyclic group containing 1-4 nitrogen atoms [for example pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, homopiperazinyl and the like]; saturated heteropolycyclic group containing 1-4 nitrogen atoms such as quinuclidinyl or the like; unsaturated condensed heterocyclic group containing 1-5 nitrogen atoms, for example N-containing heterocyclic group such as indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazopydidazinyl <u>*sic: mis-spelt term?, translated as tetrazolopyridazinyl subsequently*</u> (for example tetrazolo[1,5-b]pyridazine and the like) or the like; 3-6 membered unsaturated heteromonocyclic group containing one oxygen atom, for example pyranyl, furyl and the like; 3-6 membered unsaturated heteromonocyclic group containing 1-2 sulfur atoms, for example thienyl and the like; 3-6 membered unsaturated

heteromonocyclic group containing 1-2 oxygen atoms and 1-3 nitrogen atoms, for example oxazolyl, isoxazolyl, oxadiazolyl [for example 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl and the like] or the like; 3-6 membered saturated heteromonocyclic group containing 1-2 oxygen atoms and 1-3 nitrogen atoms [for example morpholinyl and the like]; unsaturated condensed heterocyclic group containing 1-2 oxygen atoms and 1-3 nitrogen atoms [for example benzofurazanyl, benzoxazolyl, benzoxadiazolyl and the like]; 3-6 membered unsaturated heteromonocyclic group containing 1-2 sulfur atoms and 1-3 nitrogen atoms, for example thiazolyl, isothiazolyl, thiadiazolyl [for example1, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl and the like] or the like; 3-6 membered saturated heteromonocyclic group containing 1-2 sulfur atoms and 1-3 nitrogen atoms [for example thiazolidinyl and the like]; unsaturated condensed heterocyclic group containing 1-2 sulfur atoms and 1-3 nitrogen atoms [for example benzothiazolyl, benzothiadiazolyl and the like]; unsaturated condensed heterocycle group containing 1-2 oxygen atoms [for example benzofuranyl, benzodioxolyl and the like] or the like may be proposed. The preferred examples among these are 5 or 6 membered unsaturated heteromonocyclic groups containing 1-2 heteroatoms selected from nitrogen atom, sulfur atom and oxygen atom, for example pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyranyl, furyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl are proposed, and more preferably pyrrolyl, pyridyl, furyl, thienyl, oxazolyl, isoxazolyl.

(0028)

Said "heterocyclic group" may be substituted by substituents (preferably 1-3 substituents) selected among the group comprising lower alkyl and aryl, for example N-methyl pyrrolyl, methylpyridyl, methyl thienyl, methyl isoxazolyl, N-phenyl pyrrolyl, N-tolyl pyrrolyl, phenyl pyridyl, phenyl thienyl, phenyl isoxazolyl, 5-methyl-3-phenyl isoxazolyl and the like may be proposed.

(0029)

As suitable "acyl" and suitable acyl moiety in the representation of "acylamino", carboxy, esterified carboxy, carbamoyl, lower alkyl carbamoyl, lower alkyl amino lower alkyl substituted carbamoyl, heterocyclic lower alkyl substituted carbamoyl, acyl lower alkyl substituted carbamoyl, lower alkyl amino substituted carbamoyl, heterocyclic group substituted carbamoyl, lower alkanoyl, aroyl, heterocyclic carbonyl, lower alkyl sulfonyl, aryl sulfonyl and the like may be proposed.

(0030)

As esterified carboxy, substituted or unsubstituted lower alkoxycarbonyl [for example methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, butoxycarbonyl, tertiary butoxycarbonyl, hexyloxy carbonyl, 2-(dimethylamino) ethoxycarbonyl, 2-iodoethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl and the like], substituted or unsubstituted aryloxy carbonyl [for example phenoxy carbonyl, 4-nitrophenoxy carbonyl, 2-naphthyloxy carbonyl and the like], substituted or unsubstituted aryl lower alkoxycarbonyl [for example benzyloxycarbonyl, phenethyl oxycarbonyl, benzhydryl oxycarbonyl, 4-nitrobenzyl oxycarbonyl and the like] or the like are proposed, and in particularly lower alkoxycarbonyl is preferred.

(0031)

As lower alkyl carbamoyl, mono or dilower alkyl carbamoyl such as methylcarbamoyl, ethyl carbamoyl, propyl carbamoyl, dimethylcarbamoyl, diethylcarbamoyl, N-methyl-N-ethyl carbamoyl or the like may be proposed.

(0032)

As lower alkyl amino lower alkyl substituted carbamoyl, mono or dilower alkyl amino lower alkyl substituted carbamoyl such as methylaminomethyl carbamoyl, dimethylaminomethyl carbamoyl, methylamino ethyl carbamoyl, dimethylaminoethyl carbamoyl, dimethylaminopropyl carbamoyl or the like is proposed. Among these, dimethylaminoethyl carbamoyl, dimethylaminopropyl carbamoyl are particularly preferred.

(0033)

As heterocyclic lower alkyl substituted carbamoyl, lower alkyl substituted carbamoyl substituted by piperazinyl, N-methyl piperazinyl, dimethylamino piperidyl, piperidyl, morpholinyl or the like is proposed. Among these, piperidyl ethyl carbamoyl, morpholinoethyl carbamoyl are particularly preferred.

(0034)

As acyl lower alkyl substituted carbamoyl, carboxy lower alkyl carbamoyl, esterificated carboxy lower alkyl carbamoyl, carbamoyl lower alkyl carbamoyl, lower alkyl carbamoyl lower alkyl carbamoyl, lower alkanoyl lower alkyl carbamoyl, aroyl lower alkyl carbamoyl, heterocyclic carbonyl lower alkyl carbamoyl, lower alkyl sulfonyl lower alkyl carbamoyl, aryl sulfonyl lower alkyl carbamoyl and the like are proposed, and carbamoyl lower alkyl carbamoyl is preferred, and carbamoyl methyl carbamoyl is in particularly preferred.

(0035)

As lower alkyl amino substituted carbamoyl, mono- or di- lower alkyl amino carbamoyl such as methylamino carbamoyl, dimethylamino carbamoyl, ethylamino carbamoyl, diethylamino carbamoyl or the like are proposed, and dimethylamino carbamoyl is particularly preferred.

(0036)

As heterocyclic group substituted carbamoyl, carbamoyl substituted by piperazinyl, N-methyl piperazinyl, dimethylamino piperidyl, pyrrolyl, pyridyl, piperidyl, morpholinyl or quinuclidinyl or the like is proposed. Among these, pyridyl carbamoyl, piperidyl carbamoyl, morpholinyl carbamoyl, quinuclidinyl carbamoyl are particularly preferred.

(0037)

As lower alkanoyl, substituted or unsubstituted formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl or the like may be proposed, and among these, formyl, acetyl are particularly preferred. As aroyl, substituted or unsubstituted benzoyl, naphthoyl, toluoyl, xyloyl, ditertiary butyl benzoyl, tolyl benzoyl, aminobenzoyl, tolyl benzoylamino benzoyl or the like may be proposed.

(0038)

As heterocyclic moiety in the representation of "heterocyclic carbonyl", the groups exemplified in above may be proposed. For example piperazinyl carbonyl, N-methyl piperazinyl carbonyl, dimethylamino piperidyl carbonyl, pyrrolyl carbonyl, pyridyl carbonyl, piperidyl carbonyl, morpholinyl carbonyl, quinuclidinyl carbonyl and the like may be proposed. As lower alkyl sulfonyl, methylsulfonyl, ethylsulfonyl, propyl sulfonyl, butylsulfonyl or the like are proposed, and methylsulfonyl is particularly preferred. As aryl sulfonyl, substituted or unsubstituted phenylsulfonyl, tolylsulfonyl, dimethoxyphenyl sulfonyl or the like may be proposed, and phenylsulfonyl is particularly preferred.

(0039)

As ideal "lower alkenyl", straight or branched chain 2-6C alkenyl such as vinyl, 1-propenyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl or the like may be proposed. Among these, 2-4C alkenyl such as vinyl, 1-propenyl, allyl, isopropenyl, 1-butenyl, 2-butenyl or the like is particularly preferred. Said "lower alkenyl" may be substituted by substituent (preferably 1-3 substituents) selected from the group

comprising cyano and aryl, and for example (2-methylphenyl) vinyl, 1-cyano-2,2-diphenyl vinyl and the like may be proposed.

(0040)

As ideal "lower alkylene", straight or branched chain 1-4C alkylene such as methylene, ethylene, trimethylene or the like is proposed. Among these, 1-2C alkylene such as methylene, ethylene is particularly preferred.

(0041)

As ideal "carboxy protecting group", ordinarily used carboxy protecting group such as substituted or unsubstituted lower alkyl [for example methyl, ethyl, propyl, butyl, tertiary butyl, hexyl, 2-iodo ethyl, 2,2,2-trichloroethyl and the like], substituted or unsubstituted aryl [for example phenyl, naphthyl, 4-nitrophenyl and the like], substituted or unsubstituted aryl lower alkyl [for example benzyl, phenethyl, benzhydryl, 4-nitrobenzyl or the like] or the like is nominated.

(0042)

Aryl represented by R3 may be substituted by substituent (preferably 1-3 substituents) selected from the group comprising lower alkyl and aryl, and for example tolyl, xylyl, mesityl, cumenyl, tolyl phenyl and the like may be proposed.

(0043)

As prefered compound (I), R1 and R2 together with adjacent carbon atoms form benzene ring, pyridine ring or thiophene, and those rings may be substituted by lower alkyl, R3 is (i) the lower alkenyl which may be substituted by the substituent selected from the group comprising cyano and aryl, (ii) aryl or (iii) the heterocyclic group which may be substituted by the substituent selected from the group comprising lower alkyl and aryl (the said heterocyclic group is selected from pyrrolyl, pyridyl, furyl, thienyl, oxazolyl and isoxazolyl), A is

(0044)

$$-\underset{\displaystyle R^{5}}{\overset{\displaystyle R^{4}}{\underset{|}{\overset{|}{C}}}}-CH_2-$$

(0045)

(wherein, (i) R4 and R5 are each hydrogens, (ii) R4 is a hydrogen and R5 is hydroxy or lower alkyl amino, or (iii) R4 and R5 link together to form oxo), E is lower alkylene or phenylene, X is CH or N, and Y is a single bond or

(0046)

$$\begin{array}{c} R^6 \quad O \\ | \quad \;\; \| \\ -N-C- \end{array}$$

(0047)

(wherein, R6 is (i) hydrogen, (ii) tolyl benzoyl or (iii) the amino which may be substituted by lower alkyl or acyl (the said acyl is selected from lower alkoxy carbonyl, lower alkanoyl, aroyl, lower alkyl sulphonyl and aryl sulphonyl)). Wherein, when Y is a single bond or

(0048)

$$\begin{array}{r} O \\ \| \\ -NH-C- \end{array}$$

(0049)

then 1) R1 and R2 form pyridine ring or thiophene ring together with adjacent nitrogen atom, and those rings may be substituted by lower alkyl,

2) R3 is a lower alkenyl which may be substituted by the substituent selected from the group comprising cyano and aryl or heterocyclic group substituted by the substituent selected from the group comprising lower alkyl and the aryl, or

3) E is a phenylene.

(0050)

The suitable pharmaceutically acceptable salt of target compound (I) is conventionally used non-toxic salt, and examples thereof include acid addition salt such as inorganic acid addition salt (for example hydrochloride, hydrobromide, sulfate, phosphate and the like), organic acid addition salt (for example formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate and the like), metallic salt such as alkaline metal salt (for example sodium salt, potassium salt or the like), alkaline earth metal salt (for example calcium salt, magnesium salt or the like) and the like.

(0051)

A process for the production of a target compound (I) is described below in greater detail.

Process 1

Target compound (I) or salts thereof can be produced by reacting compound (II) or salts thereof with compound (III) or reactive derivative of carboxy-group thereof or salt thereof. The same salts as those exemplified in compound (I) may be nominated as suitable salts of compounds (I), (II) and (III) and reactive derivative of carboxy-group thereof.

(0052)

As suitable reactive derivative of carboxy-group of compound (III), acid halide, acid anhydride including intramolecular acid anhydride, intermolecular acid anhydride and mixed acid anhydride, active amide, active ester and the like may be proposed. As ideal example of said reactive derivative, acid chloride; acid azide; mixed acid anhydride with acid such as substituted phosphoric acid (for example dialkyl phosphoric acid, phenyl phosphoric acid, diphenyl phosphoric acid, dibenzyl phosphoric acid, phosphoric acid halide and the like), dialkyl phosphorous acid, sulphurous acid, thiosulfuric acid, sulphuric acid, sulfonic acid (for example methanesulfonic acid and the like), aliphatic carboxylic acid (for example acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethyl butyric acid, trichloroacetic acid and the like), aromatic carboxylic acid (for example benzoic acid and the like) or the like; symmetric acid anhydride; active amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; active ester (for example cyanomethyl ester, methoxymethyl ester, dimethyl imino methyl [(CH3)2N+=CH-] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesyl phenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester or the like) or ester with N-hydroxy compound (for example N,N-dimethyl hydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxy succinimide, 1-hydroxy-1H-benzotriazole or the like) and the like may be proposed. These reactive derivatives can be suitably selected corresponding to species of used compound (III).

(0053)

Reaction is carried out usually in the conventionally used solvent, for example water, alcohol (for example methanol, ethanol and the like), acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or other arbitrary solvent which does not give bad influence to reaction. These conventionally used solvent may be used as mixture with water.

(0054)

In this reaction, when compound (III) is used in a form of free acid or in a form of salts thereof, reaction is preferably carried out in the presence of conventionally used condensing agent such as N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethyl carbodiimide, N-cyclohexyl-N'-(4-diethylamino cyclohexyl)

carbodiimide, N,N'-diethyl carbodiimide, N,N'-diisopropyl carbodiimide, N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide, N,N'-carbonyl bis(2-methyl imidazole), pentamethylene ketene-N-cyclohexyl imine, diphenylketene-N-cyclohexyl imine, ethoxyacetylene, 1-alkoxy-1-chloroethylene, trialkyl phosphite, ethyl polyphosphate, isopropyl polyphosphate, phosphorus oxychloride (phosphoryl chloride), phosphorus trichloride, diphenyl phosphoryl azide, diphenyl chlorophosphate, diphenylphosphinic acid chloride, thionyl chloride, oxalyl chloride, alkyl haloformate (for example ethyl chloroformate, isopropyl chloroformate and the like), triphenylphosphine, 2-ethyl-7-hydroxybenzisoxazolium salt, 2-ethyl-5-(m-sulphophenyl) isoxazolium hydroxide inner salt, 1-(p-chlorobenzene sulphonyloxy)-6-chloro-1H-benzotriazole, so-called Vilsmeier reagent (prepared by reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride or the like).

(0055)

The reaction can be also carried out in the presence of inorganic or organic base such as alkali metal bicarbonate, tri lower alkyl amine, pyridine, 4-dimethylaminopyridine, N-lower alkyl morpholine, N,N-dilower alkyl aniline (for example N, N-dimethylaniline and the like), N,N-di lower alkyl benzylamine or the like. The reaction temperature is not restricted in particular, and usually reaction is carried out while heating or cooling.

(0056)

Process 2

Target compound (Ia) or salts thereof can be produced by reacting compound (IV) or salts thereof with compound (V) or reactive derivative of carboxy-group thereof or salt thereof. The same salts as those exemplified in compound (I) may be nominated as suitable salts of compounds (Ia), (IV) and (V) and reactive derivative of carboxy-group thereof. This reaction can be carried out in substantially the same way as process 1 and accordingly, explanation in process 1 may be referred to for reaction system and reaction condition of this reaction (for example solvent, the reaction temperature and the like). In this reaction, compound (Ia) wherein R6a is tolyl benzoyl and R3 is tolyl phenyl can be obtained using the compound (IV) wherein R6a is hydrogen and compound (V) wherein R3 is tolyl phenyl. In this case, 2 equivalents to excess amount of compound (V) may be used with respect to compound (IV).

(0057)

Process 3

Target compound (Ib) or salts thereof can be produced by reacting compound (II) or salts thereof with compound (IIIa) or reactive derivative of carboxy-group thereof or salt thereof. The same salts as those exemplified in compound (I) may be nominated as suitable salts of compounds (Ib), (II) and (IIIa) and reactive derivative of carboxy-group thereof. This reaction can be carried out in substantially the same way as process 1 and accordingly, explanation in process 1 may be referred to for reaction system and reaction condition of this reaction (for example solvent, the reaction temperature and the like).

(0058)

Process 4

Target compound (Ic) or salts thereof may be produced by subjecting compound (Ib) or salts thereof to deacylation reaction. As suitable salts of compounds (Ib) and (Ic), the same salts as those exemplified in compound (I) may be proposed. This reaction is carried out according to normal method such as hydrolysis or the like. Preferably hydrolysis is carried out in the presence a base or acid including Lewis acid. As suitable base, inorganic base and organic base such as alkali metal (for example lithium, sodium, potassium and the like), alkaline earth metal (for example magnesium, calcium and the like), hydroxide or carbonate or bicarbonate of these, trialkylamine (for example trimethylamine, triethylamine and the like), picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1, 8-diazabicyclo[5.4.0]undec-7-ene or the like may be proposed. As suitable acid, organic acid (for example formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid and the like), inorganic acid (for example hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and the like) and Lewis acid (for example boron tribromide and the like) and the like may be nominated. Reaction is usually carried out in the solvent such as water, alcohol (for example methanol, ethanol and the like), xylene, diethylene glycol monomethyl ether, methylene chloride, tetrahydrofuran, mixture thereof, or the other arbitrary solvent which does not have bad influence on reaction. Liquid base or acid is usable as solvent. The reaction temperature is not restricted in particular, and usually reaction is carried out while heating or cooling.

(0059)

Process 5

Target compound (Id) or salts thereof can be produced by reacting compound (Ic) or salts thereof with alkylating agent. As suitable salts of compounds (Ic) and (Id), the same salts as those exemplified in compound (I) may be proposed. As suitable alkylating agent, a lower alkyl halide (for example methyl iodide, ethyl iodide and the like), aliphatic ketone

(for example acetone, ethyl methyl ketone and the like), carboxaldehyde (for example formaldehyde, ethanal and the like), orthocarboxylate (for example triethyl orthoformate and the like) or combination of carbonyl compound with reducing agent including ones for chemical reduction and catalytic reduction (for example formic acid, sodium borohydride, sodium cyanoborohydride, palladium carbon and the like) may be proposed. When lower alkyl halide is used as alkylating agent, it is preferably carried out in the presence of a base such as alkali metal (for example sodium, potassium and the like) alkaline earth metal (for example magnesium, calcium and the like), hydride, hydroxide, carbonate or bicarbonate of these, tri lower alkyl amine, N,N-di lower alkyl aniline or the like. Reaction is usually carried out in conventionally used solvent which does not exert a harmful effect on reaction, for example water, dioxane, alcohol (for example methanol, ethanol and the like), acetonitrile, tetrahydrofuran, acetic acid, N,N-dimethylformamide or mixture thereof. Moreover, when the aforesaid alkylating agent or base is liquid form, it can be used as solvent. The reaction temperature is not restricted in particular, and reaction can be carried out while heating or cooling.

(0060)

Process 6

Target compound (Ib) or salts thereof can be produced by reacting compound (Ic) or salts thereof with acylating agent. As suitable salts of compounds (Ib) and (Ic), the same salts as those exemplified in compound (I) may be proposed. As acylating agent, organic acid represented by formula R8-OH (wherein R8 is acyl described with reference to examples above) or reactive derivative thereof may be proposed. As suitable reactive derivative of said organic acid, conventionally used one such as acid halide (for example acid chloride, acid bromide and the like), acid azide, acid anhydride, active amide, active ester or the like may be proposed. When free acid is used as acylating agent, acylation reaction is preferably carried out in the presence of conventionally used condensing agent such as N,N'-dicyclohexylcarbodiimide or the like. The reaction is carried out usually in the conventionally used solvent, for example water, acetone, dioxane, chloroform, methylene chloride, acetonitrile, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine, other arbitrary organic solvent which does not give bad influence to reaction or a mixture thereof. Reaction is also preferred to be carried out in the presence of conventionally used base such as triethylamine, pyridine, sodium hydroxide or the like. The reaction temperature is not restricted in particular, and reaction can be carried out while heating or cooling.

(0061)

Process 7

Target compound (If) or salts thereof can be produced by reacting compound (Ic) or salts thereof with reducing agent. As suitable salts of compounds (Ic) and (If), the same salts as those exemplified in compound (I) may be proposed. As suitable reducing agent, alkali metal borohydride (for example sodium borohydride and the like) and the like may be proposed. The reaction is carried out usually in conventionally used solvent, for example alcohol (for example methanol, ethanol and the like), water or other arbitrary solvent which does not give bad influence to reaction or mixture thereof. The reaction temperature is not restricted in particular, and reaction can be carried out while heating or cooling.

(0062)

Process 8

Target compound (Ig) or salts thereof can be produced by reacting compound (Ic) or salts thereof with compound (VI) or salts thereof, and then subjecting to reductive reaction. As suitable salts of compound (VI), the acid addition salt exemplified in compound (I) may be proposed. As suitable salts of compounds (Ic) and (Ig), the same salts as those exemplified in compound (I) may be proposed. Reaction of compound (Ie) or salts thereof and compound (VI) or salts thereof is performed in the absence of solvent or in the suitable solvent in the presence or absence of dehydrating agent. As dehydrating agent, it is possible to use desiccant used for dehydration of ordinary solvent such as molecular sieve, mineral acid such as hydrochloric acid, sulphuric acid, boron trifluoride or the like, organic acid such as p-toluenesulfonic acid or the like, or mixture thereof. Reaction is carried out usually in conventionally used solvent which does not exert a harmful effect on reaction, for example alcohol (for example methanol, ethanol, isopropanol and the like), benzene, toluene, xylene, dichloromethane, dichloroethane, chloroform, carbon tetrachloride, N,N-dimethylformamide, dimethylacetamide, N-methylpyrrolidone or mixture thereof. The reaction temperature is not restricted in particular, and reaction is carried out usually at room temperature or while heating. The quantity of compound (VI) used is not restricted in particular and usually, equimolar to large excess of compound (VI) may be used with respect to compound (Ie). As the quantity of dehydrating agent used, large excess may be used in case of desiccant, and catalytic quantity may be used in case of acid.

(0063)

As for subsequent reductive reaction, various kinds of processes such as catalytic reduction, chemical reduction and the like can be applied. As suitable catalyst used in

catalytic reduction, for example palladium, palladium black, palladium carbon, platinum, platinum oxide, copper chromite, Raney nickel and the like may be proposed. Usually this reductive reaction is carried out in conventionally used solvent which does not exert a harmful effect on reaction, for example water, acetic acid, alcohol (for example methanol, ethanol, isopropanol and the like), hexane, cyclohexane, diethylene glycol dimethylether, dioxane, tetrahydrofuran, diethyl ether, ethyl acetate, methyl acetate, N,N-dimethylformamide or mixture thereof. The reaction temperature is not restricted in particular, and usually reaction is carried out while heating or cooling.

(0064)

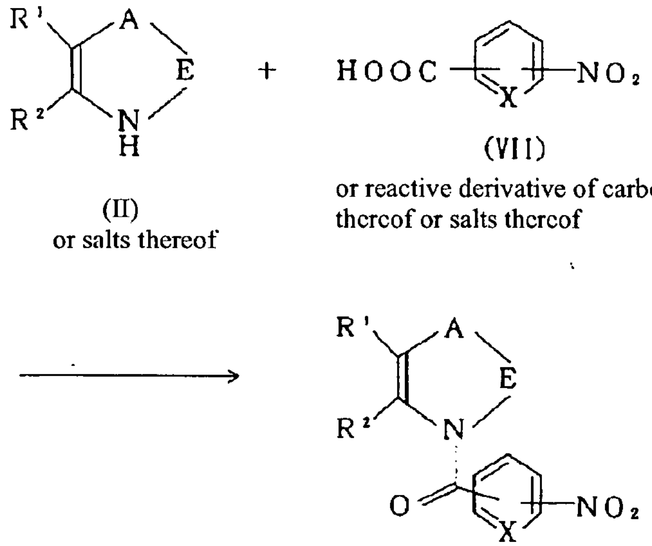
As the suitable reducing agent used in chemical reduction, for example hydride reducing agent such as lithium aluminium hydride, sodium borohydride, diborane and the like may be proposed. Usually this reductive reaction is carried out in conventionally used solvent which does not exert a harmful effect on reaction, for example water, alcohol (for example methanol, ethanol, isopropanol and the like), tetrahydrofuran, diethyl ether, diglyme, dimethylformamide or mixture thereof. The reaction temperature is not restricted in particular, and usually carried out while heating or cooling. Preferably reduction method using hydride reducing agent is applied. Moreover, by reacting compound (Ig) wherein R5a is mono lower alkyl amino with alkylating agent, compound (Ig) wherein R5a is di lower alkyl amino can be produced. This alkylation reaction can be carried out in substantially the same way as process 5 and accordingly, explanation in process 5 may be referred to for reaction system and reaction condition of this reaction (for example solvent, the reaction temperature and the like).

(0065)

Starting compound (IV), (IIIa) and compound (IIIb) wherein Y in compound (III) is -NH-CO- or salts thereof can be prepared using the following various processes.

(0066)

Process A



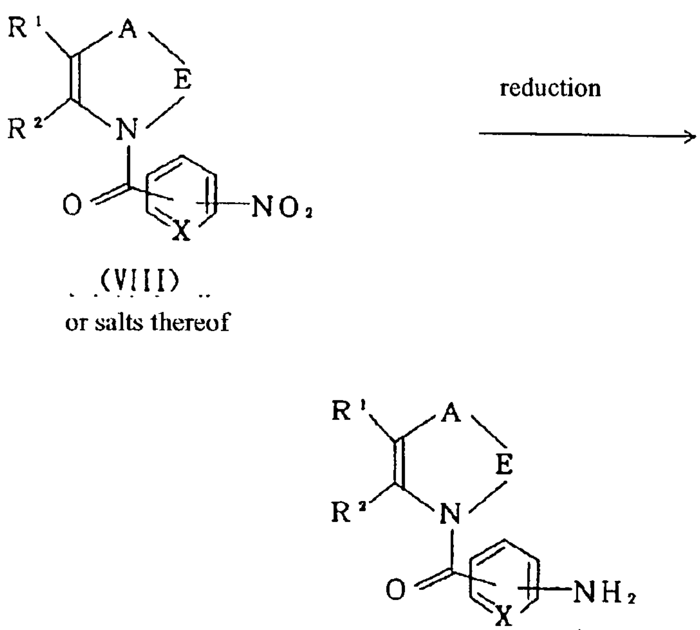
(II)
or salts thereof

(VII)
or reactive derivative of carboxy-group thereof or salts thereof

(VIII)
or salts thereof

(0067)

Process B

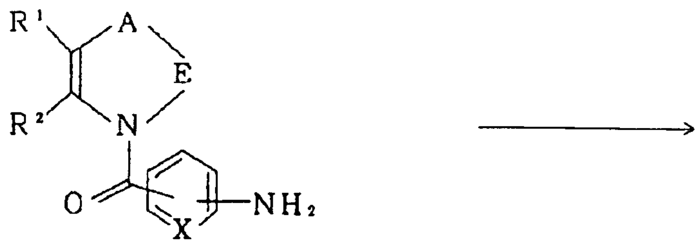


(VIII)
or salts thereof

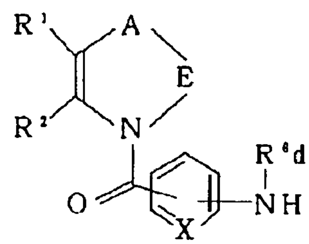
(IVa)
or salts thereof

(0068)

Process C



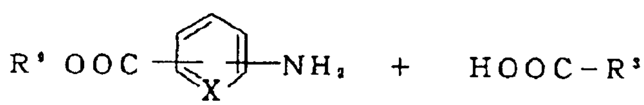
(VI a)
or salts thereof



(IVb)
or salts thereof

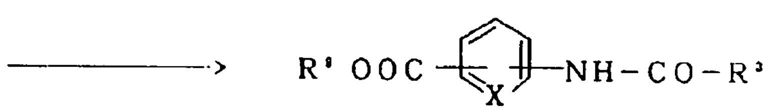
(0069)

Process D



(IX)
or salts thereof

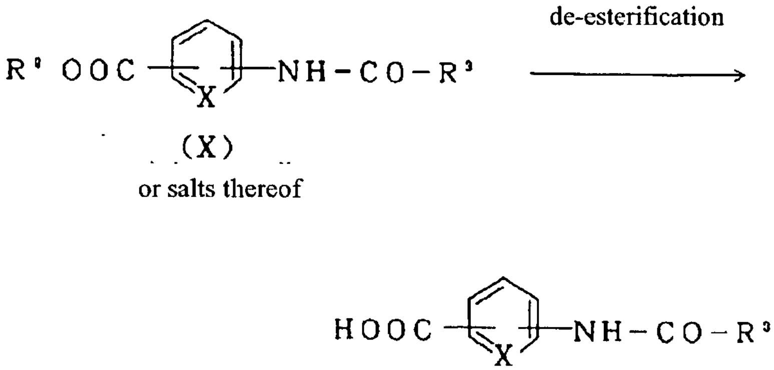
(V)
or reactive derivative of carboxy-group thereof or salts thereof



(X)
or salts thereof

(0070)

Process E

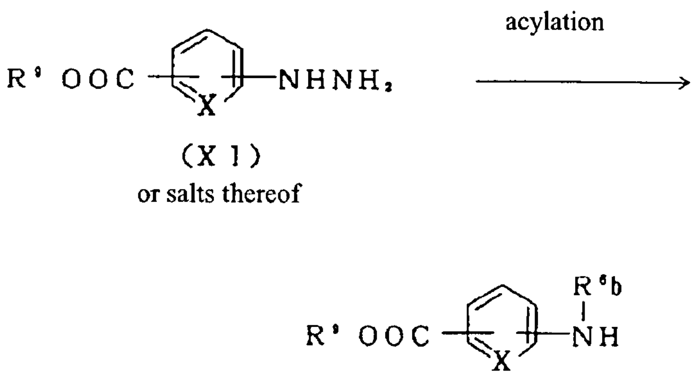


(X)
or salts thereof

(IIIb)
or salts thereof

(0071)

Process F

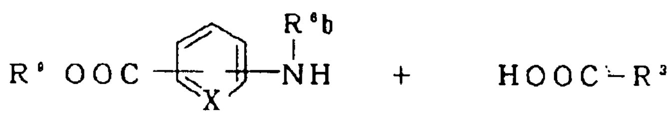


(XI)
or salts thereof

(XII)
or salts thereof

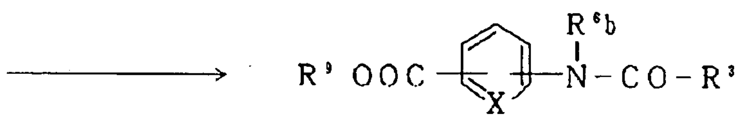
(0072)

Process G



(XII) or salts thereof

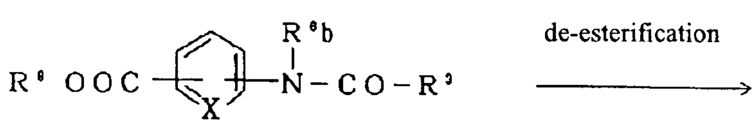
(V) or reactive derivative of carboxy-group thereof or salts thereof



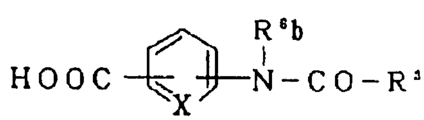
(XIII) or salts thereof

(0073)

Process H



(XIII) or salts thereof



(IIIa) or salts thereof

(0074)

Wherein in the aforesaid reaction formulae, R1, R2, R3, A, E, X and R6b are the same as aforesaid respective definition, and R6d is tolyl benzoyl and R9 is carboxy protecting group. Preparation method of the said starting compound is described below in greater detail.

(0075)

Process A

Compound (VIII) or salts thereof can be produced by reacting compound (II) or salts thereof with compound (VII) or reactive derivative of carboxy-group thereof or salt thereof. The same salts as those exemplified in compound (I) may be nominated as suitable salts of compounds (II), (VIII) and (VII) and reactive derivative of carboxy-group thereof. This reaction can be carried out in substantially the same way as process 1 and accordingly, explanation in process 1 may be referred to for reaction system and reaction condition of this reaction (for example solvent, the reaction temperature and the like).

(0076)

Process B

Compound (IVa) wherein R6a is hydrogen in compound (IV) or salts thereof can be produced by subjecting compound (VIII) or salts thereof to reduction. As suitable salts of compounds (IVa) and (VIII), the same salts as those exemplified in compound (I) may be proposed. Reduction includes chemical reduction and catalytic reduction, and it is carried out in accordance with normal methods. The reducing agent suitable to be used in chemical reduction comprises metal (for example tin, zinc, iron and the like), combination of such metal and/or metal compound (for example chlorochromate, chromium acetate and the like) with organic acid or inorganic acid (for example formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid and the like), combination of such aforesaid metal and/or metal compound with base (for example ammonia, ammonium chloride, sodium hydroxide and the like), metal hydride compound such as aluminium hydride compound (for example lithium aluminium hydride, sodium aluminum hydride, aluminium hydride, lithium trimethoxy aluminium hydride, tri-t-butoxy aluminum hydride and the like), boron hydride compound (for example sodium borohydride, lithium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, borane, diborane and the like) or the like, phosphorus compound (for example phosphorus trichloride, phosphorus tribromide, triphenylphosphine, triethylphosphine and the like) or the like.

(0077)

The suitable catalyst to be used in catalytic reduction is conventionally used one such as platinum catalyst (for example platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire and the like), palladium catalyst (for example

spongy palladium, palladium black, palladium oxide, palladium carbon, colloidal palladium, palladium / barium sulfate, palladium / barium carbonate and the like), nickel catalyst (for example reduced nickel, nickel oxide, Raney nickel and the like), cobalt catalyst (for example reduced cobalt, Raney cobalt and the like), iron catalyst (for example reduced iron, Raney iron and the like), copper catalysis (for example reduced copper, Raney copper, Ullmann copper and the like) or the like. Reduction is carried out usually in solvent. As the suitable solvent to be used, water, alcohol (for example methanol, ethanol, propanol and the like), acetonitrile, other conventionally used organic solvent such as diethyl ether, dioxane, tetrahydrofuran or the like or a mixture thereof may be nominated. The reaction temperature is not restricted in particular, and preferably reaction is carried out while heating or cooling.

(0078)

Process C

Compound (IVb) wherein R6a is tolyl benzoyl in compound (IV) or salts thereof can be produced by reacting compound (IVa) or salts thereof with tolyl benzoic acid or reactive derivative of carboxy-group thereof or salt thereof. As suitable salts of compounds (IVa) and (IVb), the same salts as those exemplified in compound (I) may be proposed. As suitable salt of tolyl benzoic acid and reactive derivative of carboxy-group thereof, alkali metal salt or alkaline earth metal salt exemplified in compound (I) may be nominated. This reaction can be carried out in substantially the same way as process 1 and accordingly, explanation in process 1 may be referred to for reaction system and reaction condition of this reaction (for example solvent, the reaction temperature and the like).

(0079)

Process D

Compound (X) or salts thereof can be produced by reacting compound (IX) or salts thereof with compound (V) or reactive derivative of carboxy-group thereof or salt thereof. As suitable salts of compounds (IX) and (X), inorganic acid addition salt or organic acid addition salt exemplified in compound (I) may be proposed. The same salts as those exemplified in compound (I) may be nominated as suitable salts of compound (V) and reactive derivative of carboxy-group thereof. This reaction can be carried out in substantially the same way as process 1 and accordingly, explanation in process 1 may be referred to for reaction system and reaction condition of this reaction (for example solvent, the reaction temperature and the like).

(0080)

Process E

Compound (IIIb) or salts thereof can be produced by subjecting compound (X) or salts thereof to deesterification. As suitable salt of compound (X), inorganic acid addition salt or organic acid addition salt exemplified in compound (I) may be proposed. As suitable salt of compound (IIIb), the same salts as those exemplified in compound (I) may be proposed. The reaction is carried out according to normal method such as hydrolysis, reduction or the like. Hydrolysis is preferably carried out in the presence of base or acid including Lewis acid. As suitable base, inorganic base and organic base such as alkali metal (for example lithium, sodium, potassium and the like), alkaline earth metal (for example magnesium, calcium and the like), hydroxide, carbonate or bicarbonate of these, trialkylamine (for example trimethylamine, triethylamine and the like), picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene or the like may be proposed. As suitable acid, organic acid (for example formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid and the like), inorganic acid (for example hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and the like) and Lewis acid (for example boron tribromide and the like) may be nominated. Reaction is carried out usually in the solvent such as water, alcohol (for example methanol, ethanol and the like), xylene, diethylene glycol monomethyl ether, methylene chloride, tetrahydrofuran, mixture thereof or the like or in other arbitrary solvent which does not have bad influence on reaction. Base or acid in liquid form can be used as solvent. The reaction temperature is not restricted in particular, however, reaction is usually carried out with warming or cooling.

(0081)

Reduction can be preferably applied for elimination of ester moiety such as 4-nitrobenzyl, 2-iodo ethyl, 2,2,2-trichloroethyl or the like. As the reduction method which can be applied for the said elimination reaction, chemical reduction and catalytic reduction may be proposed. The suitable reducing agent to be used in chemical reduction is metal (for example tin, zinc, iron and the like) or metal compound (for example chlorochromate, chromium acetate and the like) in a combination with organic acid or inorganic acid (for example formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid and the like). The suitable catalyst to be used in catalytic reduction is conventionally used one such as platinum catalyst (for example platinum plate, spongy platinum, platinum black, platinum colloid, platinum oxide, platinum line and the like), palladium catalyst (for example spongy palladium, palladium black, palladium oxide, palladium carbon, palladium colloid, palladium / barium sulfate, palladium / barium carbonate and the like), nickel catalyst (for example reduced nickel,

nickel oxide, Raney nickel and the like), cobalt catalyst (for example reduced cobalt, Raney cobalt and the like), iron catalyst (for example reduced iron, Raney iron and the like), copper catalyst (for example reduced copper, Raney copper, Ullmann copper and the like) or the like. Reduction is carried out usually in the conventionally used solvent which does not exert a harmful effect on reaction such as water, alcohol (for example methanol, ethanol, propanol and the like), N,N-dimethylformamide, mixture thereof or the like. Moreover, when the acid used in the aforesaid chemical reduction is liquid form, it can be used as solvent. Moreover as the solvent suitable used in catalytic reduction, the aforesaid solvent or other conventionally used solvent such as diethyl ether, dioxane, tetrahydrofuran or the like, or mixtures thereof may be proposed. The reaction temperature of this reduction is not restricted in particular, however, reaction is usually carried out with warming or cooling.

(0082)

Process F

Compound (XII) or salts thereof can be produced by subjecting compound (XI) or salts thereof to acylation reaction. As suitable salts of compounds (XI) and (XII), inorganic acid addition salt or organic acid addition salt exemplified in compound (I) may be proposed. This reaction can be carried out in substantially the same way as process 6 and accordingly, explanation in process 6 may be referred to for reaction system and reaction condition of this reaction (for example solvent, the reaction temperature and the like).

(0083)

Process G

Compound (XIII) or salts thereof can be produced by reacting compound (XII) or salts thereof with compound (V) or reactive derivative of carboxy-group thereof or salt thereof. As suitable salt of compound (XII), inorganic acid addition salt or organic acid addition salt exemplified in compound (I) may be proposed. The same salts as those exemplified in compound (I) is nominated as suitable salt of compound (XIII) and (V), and reactive derivative of carboxy-group thereof. This reaction can be carried out in substantially the same way as process 1 and accordingly, explanation in process 1 may be referred to for reaction system and reaction condition of this reaction (for example solvent, the reaction temperature and the like).

(0084)

Process H

Compound (IIIa) or salts thereof can be produced by subjecting compound (XIII) or salts thereof to deesterification. As suitable salt of compound (IIIa) and (XIII), the same salts as those exemplified in compound (I) may be proposed. This reaction can be carried out in substantially the same way as process E and accordingly, explanation in process E may be referred to for reaction system and reaction condition of this reaction (for example solvent, the reaction temperature and the like).

(0085)

Compound obtained by the aforesaid various processes can be purified by normal methods, for example pulverization, recrystallization, column chromatography, reprecipitation and the like, and in accordance with requirements, it can be converted to desired salt by normal method. Stereoisomers of compound (I) and other compounds, such as geometric isomers and optical isomers due to asymmetric carbon and double bond, or the like, may exist but such isomers and mixtures thereof are all included in the range of this invention.

(0086)

Target compound (I) and pharmacologically acceptable salts thereof have activity such as vasopressin antagonism, vasodilator action, antihypertensive action, action of inhibiting release of carbohydrate from liver, mesangial cell proliferation inhibitory action, diuresis action, platelet aggregation inhibitory action, oxytocin antagonism or the like, and is useful as therapy and/or preventive agent for hypertension, cardiac failure, renal failure, edema, ascites, inappropriate vasopressin secretion syndrome, liver cirrhosis, hyponatremia, hypokalemia, diabetes mellitus, circulatory failure, oxytocin associated disease (for example premature delivery, dysmenorrhea, endometritis and the like) or the like in a human and animal. Pharmacology data of compound (I) is shown below in order to illustrate usefulness of target compound (I).

(0087)

Test 1

<u>Vasopressin 1 (V1) receptor binding test</u>

(i) Test process

Liver of rat is shredded, and it is homogenised in 10 times its volume of ice cooled 250 mM sucrose buffer containing 25 mM Tris-HCl (pH7.4), 5 mM MgCl2 and 0.1 mM phenylmethyl sulphonyl fluoride (PMSF). Homogenate is centrifuged and separated at 1000 x g for ten minutes. Supernatant fraction is separated, and it is centrifuged and separated at 45000 x g for 30 minutes. Remaining pellet is suspended in 10 times its

volume of ice cooled 100 mM Tris-HCl (pH7.4) buffer (containing 5 mM MgCl2, 0.1 % bovine serum albumin and 0.1 mM PMSF), and it is centrifuged and separated again at 45000 x g for 30 minutes. The last pellet is resuspended in 100 mM Tris-HCl buffer. The obtained membrane sample is used for binding test promptly.

(0088)

Competitive assay is carried out using 0.5 nM ^{3}H-vasopressin ([phenylalanyl-3,4,5-^{3}H]-vasopressin; 40-87 Ci/mmol; New England Nuclear) in 100 mM Tris-HCl (pH7.4) buffer in equilibrium state (25°C for 60 minutes). Non-specific binding is measured using 1 μM [d(CH2)5, Tyr^2(Me), Arg^8] vasopressin (Peptide Institute, Japan). After incubation, reaction is terminated by the addition of 5 ml of ice cooled 100 mM Tris-HCl (pH7.4) buffer, and filtration is carried out promptly by passing through Whatman glass filter (GF/C). Filter is washed two times with the same buffer (5 ml). Glass filter is mixed with liquid scintillation cocktail, and the radioactivity is measured in liquid scintillation counter (Tri-Carb 4530, Packard). Competitive activity of the test compound is expressed by IC_{50} value.

(ii) Test result

(0089)

Table 1

Test compound (Example No.)	IC_{50} (M)
1-1)	2.2×10^{-8}

(0090)

Test 2

Vasopressin 2 (V2) receptor bond test

(i) Test process

Medullary papilla of kidney of male rat is shredded and homogenised in 10 times the volume of ice cooled 250 mM sucrose buffer containing 25 mM Tris-HCl (pH7.4), 5 mM MgCl2 and 0.1 mM phenylmethyl sulphonyl fluoride (PMSF). Homogenate is centrifuged and separated at 500 x g for five minutes. Supernatant fraction is separated and recovered, and is centrifuged and separated at 45000 x g for 30 minutes. Remaining pellet is resuspended in 10 times the volume of ice cooled 100 mM Tris-HCl (pH7.4) buffer (containing 5 mM MgCl2, 0.1 % bovine serum albumin and 0.1 mM PMSF), and it is centrifuged and separated at 45000 x g once again for 30 minutes. The last pellet is

resuspended in 100 mM Tris-HCl buffer. The obtained membrane sample is used for binding test promptly.

(0091)

Competitive assay is carried out using 0.5 nM^{3}H-vasopressin ([phenylalanyl-3,4,5-^{3}H]-vasopressin; 40-87 Ci/mmol; New England Nuclear) in 100 mM Tris-HCl (pH7.4) buffer in equilibrium state (20°C for 60 minutes). Non-specific binding is measured using 1 μM [d(CH2)5, D-Ile^2, Ile^4, Arg^8] vasopressin (Penisula Laboratory USA). After incubation, reaction is terminated by the addition of 5 ml of ice cooled 100 mM Tris-HCl (pH7.4) buffer, and filtration is carried out promptly by passing through Whatman glass filter (GF/C). Filter is washed two times with the same buffer (5 ml). Glass filter is mixed with liquid scintillation cocktail, and the radioactivity is measured in liquid scintillation counter (Tri-Carb 4530, Packard). Competitive activity of the test compound is expressed by IC_{50} value.

(ii) Test result

(0092)

Table 2

Test compound (Example No.)	IC_{50} (M)
1-1)	4.9×10^{-8}

(0093)

The compounds of this invention (I) can be used in the form of a drug preparation for therapy. Said drug preparation contains any of the said compounds as active ingredient in a form of mixture of pharmacologically acceptable solid, semisolid or liquid organic or inorganic excipient suitable for oral administration, parenteral administration or external use (local application). As drug preparation, encapsulated formulation, tablet, sugar-coated tablet, granule, suppository, liquid agent, lotion agent, suspension, emulsion, ointment, gel agent or the like may be proposed. In accordance with requirement, it is possible to formulate adjuvant, supporting substance, stabilizer, wetting agent or emulsifier, buffer agent, or other conventional additive in these preparations.

(0094)

Dose of compound (I) differs by age and symptom of patient, however, about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg as average per dose of

compound (I) will be effective in therapy of the aforesaid various diseases. Generally administration may be carried out in an amount between 0.1 mg/individual and about 1000 mg/individual per day.

(0095)

The following Production Examples, Reference Example and Examples are shown in order to explain this invention.

(0096)

Production Example 1

To 2-(5-nitro) furancarboxylic acid (785mg) dissolved in dichloromethane (20 ml) were added oxalyl chloride (0.523 ml) and several drops of N,N-dimethylformamide, and the mixture was stirred at room temperature for two hours. The solvent was eliminated by distillation under reduced pressure, and the thereby obtained oily substance was added to dichloromethane (20 ml) solution of mixture of 1,2,3,4-tetrahydroquinoline (799 mg) and triethylamine (0.836 ml). The mixture was stirred at room temperature for two hours, and the solution was washed with dilute hydrochloric acid and aqueous sodium chloride, and drying was carried out with magnesium sulfate. The solvent was eliminated by distillation under reduced pressure, and the thereby obtained oily substance was purified by silica gel column chromatography (eluate; n-hexane : ethyl acetate = 4 : 1), and 1-[2-(5-nitro) furoyl]-1,2,3,4-tetrahydroquinoline (1.25 g) was obtained.

NMR ($CDCl_3$, δ): 2.06 (2H, tt, J = 6, 6 Hz), 2.82 (2H, t, J = 6 Hz), 3.92 (2H, t, J = 6 Hz), 6.77 (1H, d, J = 4 Hz), 6.90 (1H, d, J = 7.5 Hz), 7.05 (1H, d, J = 7.5 Hz), 7.16 (1H, d, J = 7.5 Hz), 7.21-7.29 (2H, m).

(0097)

Production Example 2

The mixture wherein methyl 6-aminonicotinate•hydrochloride (450 mg) and 2,3-dimethylbenzoyl chloride (402 mg) were added to 10 ml pyridine was stirred overnight at room temperature. Pyridine was eliminated by distillation under reduced pressure, and the residue was dissolved in chloroform. This chloroform solution was washed with water and aqueous sodium chloride and drying was carried out with magnesium sulfate. The solvent was eliminated by distillation under reduced pressure, and the residue was treated by silica gel column chromatography (eluate; chloroform), and methyl 6-(2,3-dimethylbenzoylamino)nicotinate (391 mg) was obtained.

NMR ($CDCl_3$, δ): 2.30 (3H, s), 2.46 (3H, s), 3.92 (3H, s), 7.15 (1H, dd, J = 7.5, 7.5 Hz), 7.25 (1H, d, J = 7.5 Hz), 7.32 (1H, d, J = 7.5 Hz), 8.32 (1H, dd, J = 8.5, 2 Hz), 8.48 (1H, d, J = 8.5 Hz), 8.50 (1H, d, J = 2 Hz), 9.19 (1H, br s).

(0098)

Production Example 3

Triethylamine (2.80 ml) and di-t-butyl dicarbonate (2.19 g) were added to methyl 4-hydrazinobenzoate hydrochloride (815 mg) dissolved in dichloromethane (60 ml), and the mixture was stirred overnight at room temperature. This solution was washed sequentially with dilute hydrochloric acid, sodium bicarbonate aqueous solution and aqueous sodium chloride, and drying was carried out with magnesium sulfate. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluate; chloroform) and methyl 4-(2-t-butoxycarbonyl)hydrazinobenzoate (836 mg) was obtained.

NMR ($CDCl_3$, δ): 1.42 (9H, s), 3.87 (3H, s), 6.01 (1H, br), 6.43 (1H, br), 6.80 (2H, d, J = 8.5 Hz), 7.90 (2H, d, J = 8.5 Hz).

(0099)

Production Example 4

Triethylamine (0.27 ml) and 2,3-dimethylbenzoyl chloride (321 mg) were added to dichloromethane (15 ml) solution of methyl 4-(2-t-butoxycarbonyl)hydrazinobenzoate (416 mg) obtained in Production Example 3, and the mixture was stirred at room temperature for 72 hours. This solution was washed sequentially with dilute hydrochloric acid, saturated aqueous sodium bicarbonate solution and aqueous sodium chloride, and drying was carried out with magnesium sulfate. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluate; n-hexane : ethyl acetate = 5 : 1) and methyl 4-[2-t-butoxycarbonyl-1-(2,3-dimethylbenzoyl)hydrazino]benzoate (571 mg) was obtained.

NMR ($CDCl_3$, δ): 1.43 (9H, s), 2.21 (3H, s), 2.28 (3H, s), 3.88 (3H, s), 6.88-7.30 (5H, m), 7.82-8.01 (3H, m).

(0100)

Production Example 5

Triethylamine (1.68 ml) and acetic anhydride (0.57 ml) were added to methyl 4-hydrazino benzoate hydrochloride (1.02 g) dissolved in dichloromethane (20 ml). After stirring overnight at room temperature, the mixture was washed with water and aqueous sodium chloride, and the organic layer was dried with magnesium sulfate. The solvent was

eliminated by distillation under reduced pressure, and the residue was solidified with diethyl ether, and methyl 4-(2-acetyl)hydrazinobenzoate (516 mg) was obtained.
NMR ($CDCl_3$, δ): 1.90 (2H, br), 2.07 (3H, s), 3.84 (3H, s), 6.81 (2H, d, J = 8.5 Hz), 7.90 (2H, d, J = 8.5 Hz).

(0101)

Production Example 6

Mixture of methyl 4-(2-acetyl)hydrazinobenzoate (500 mg) obtained in Production Example 5 and 2,3-dimethylbenzoyl chloride (445 mg) added to 10 ml pyridine was heated at 100° C for five hours, and the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate (20 ml) and was washed with dilute hydrochloric acid and aqueous sodium chloride. This solútion was dried with magnesium sulfate, and the solvent was eliminated by distillation under reduced pressure, and an oily substance was obtained. This oily substance was purified by silica gel column chromatography (eluate; 1 % methanol-containing chloroform), and methyl 4-[2-acetyl-1-(2,3-dimethylbenzoyl)hydrazino]benzoate (610 mg) was obtained.
NMR ($CDCl_3$, δ): 2.21 (3H, s), 2.28 (3H, s), 3.88 (3H, s), 6.92-7.13 (3H, m), 7.24 (2H, m), 7.88 (2H, d, J = 8.5 Hz), 8.02 (1H, s).

(0102)

Production Example 7

Pyridine (893 mg) was added to dichloromethane (10 ml) solution of 5,6,7,8-tetrahydro-4H-thieno[3,2-b]azepine (346 mg) and p-nitrobenzoyl chloride (462 mg) at 0° C. The obtained solution was held at room temperature for two hours. The reaction mixture was concentrated under reduced pressure, and diluted with ethyl acetate and water. Organic extract layer was washed with 1N hydrochloric acid and aqueous sodium chloride. Combined extract was dried with magnesium sulfate and concentrated. By refining the residue by silica gel column chromatography (eluate; ethyl acetate : n-hexane = 1 : 4), 4-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-4H-thieno[3,2-b]azepine (607 mg) was obtained.
NMR ($CDCl_3$, δ): 1.68-1.95 (2H, m), 1.95-2.18 (2H, m), 2.86-3.02 (2H, m), 3.58-4.17 (2H, br s), 6.14 (1H, d, J = 6 Hz), 6.68 (1H, d, J = 6 Hz), 7.42 (2H, d, J = 8 Hz), 8.08 (2H, d, J = 8 Hz).

(0103)

Production Example 8

The following compounds were obtained in the same way as in Production Example 7.

1) 2,3-dimethyl-8-(4-nitrobenzoyl)-4,5,6,7-tetrahydro-8H-thieno[2,3-b]azepin-4-one.
NMR ($CDCl_3$, δ): 2.06-2.27 (2H, m), 2.16 (3H, s), 2.22 (3H, s), 2.71-2.87 (2H, m), 4.02 (2H, br t, J = 6 Hz), 7.54 (2H, d, J = 8 Hz), 8.16 (2H, d, J = 8 Hz).

(0104)

2) 9-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-9H-pyrido[2,3-b]azepine.
NMR ($CDCl_3$, δ): 1.69-2.13 (4H, m), 2.85-3.05 (2H, m), 3.58-4.45 (2H, br s), 7.04 (1H, dd, J = 5, 8 Hz), 7.36 (2H, d, J = 9 Hz), 7.60 (1H, dd, J = 2, 8 Hz), 7.96 (1H, dd, J = 2, 5 Hz), 8.02 (2H, d, J = 9 Hz).

(0105)

3) 5-(4-nitrobenzoyl)-10,11-dihydro-5H-dibenzo[b,f]azepine.
NMR ($CDCl_3$, δ): 2.82-3.13 (2H, m), 3.47-3.76 (2H, m), 6.56-7.46 (8H, m), 7.55 (2H, d, J = 8 Hz), 8.07 (2H, d, J = 8 Hz).

(0106)

Production Example 9

The mixture of 4-(4-nitrobenzoyl)-5,6,7,8-tetrahydro-4H-thieno[3,2-b]azepine (593 mg) obtained in Production Example 7 and iron powder (1.1 g) added to acetic acid (2 ml) and ethanol (20 ml) was heated for one hour 30 minutes under reflux. The obtained mixture was filtered with celite, and the filtrate was concentrated. The residue was dissolved in ethyl acetate and washed with water and aqueous sodium chloride, and drying was carried out with magnesium sulfate. The organic layer was concentrated, and crude product was obtained, and this was pulverised in diethyl ether, and pure 4-(4-aminobenzoyl)-5,6,7,8-tetrahydro-4H-thieno[3,2-b]azepine (356 mg) was obtained.
NMR ($CDCl_3$, δ): 1.68-1.89 (2H, m), 1.89-2.11 (2H, m), 2.85-3.04 (2H, m), 3.57-4.22 (2H, br s), 6.27 (1H, d, J = 6 Hz), 6.47 (2H, d, J = 8 Hz), 6.68 (1H, d, J = 6 Hz), 7.14 (2H, d, J = 8 Hz).

(0107)

Production Example 10

8-(4-aminobenzoyl)-2,3-dimethyl-4,5,6,7-tetrahydro-8H-thieno[2,3-b]azepin-4-one was obtained in the same way as in Production Example 9 using 2,3-dimethyl-8-(4-nitrobenzoyl)-4,5,6,7-tetrahydro-8H-thieno[2,3-b]azepin-4-one obtained in Production Example 8-1).
NMR ($CDCl_3$, δ): 2.06-2.29 (2H, m), 2.17 (3H, s), 2.24 (3H, s), 2.71-2.84 (2H, m), 3.96 (2H, br t, J = 7 Hz), 6.54 (2H, d, J = 8 Hz), 7.29 (2H, d, J = 8 Hz).

(0108)

Production Example 11

To 1-(4-methylphenyl)pyrrole (925 mg) dissolved in tetrahydrofuran (20 ml) was added dropwise n-butyllithium (1.5M n-hexane solution, 4 ml) at 78° C, and this solution was stirred at the same temperature for two hours. The aforesaid solution was gradually added to mixture of dry ice and diethyl ether (50 ml) while stirring, and was washed with water and aqueous sodium chloride and drying was carried out with magnesium sulfate. The solvent was eliminated by distillation under reduced pressure, and an oily substance was obtained. This oily substance was purified by silica gel column chromatography (eluate; 2 % methanol-containing chloroform), and 1-(4-methylphenyl)pyrrole-2-carboxylic acid (550 mg) was obtained.

NMR ($CDCl_3$, δ): 2.40 (3H, s), 6.28 (1H, dd, J = 2.5, 4 Hz), 6.94 (1H, dd, J = 2.5, 2.5 Hz), 7.14-7.23 (5H, m).

(0109)

Production Example 12

Sodium hydride (800 mg in 60 % oil) was added at 0 ° C to 4-carbomethoxyphenylmethyl triphenylphosphonium chloride (8.94 g) dissolved in tetrahydrofuran (50 ml), and this solution was stirred at the same temperature for one hour 30 minutes. 2-methylbenzaldehyde (2.41 g) dissolved in tetrahydrofuran (10 ml) was added to this solution, and the mixture was stirred at room temperature for five hours. This solution was diluted with ethyl acetate (150 ml) and was washed with water and aqueous sodium chloride, and drying was carried out with magnesium sulfate. The solvent was eliminated by distillation under reduced pressure, and next n-hexane was added to the residue, and the insoluble triphenylphosphine oxide was eliminated by filtration. Filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (eluate; n-hexane : ethyl acetate = 20 : 1 - 9 : 1). Firstly, methyl 4-[(Z)-(2-methylphenyl)vinyl]benzoate (2.66 g) was obtained, and thereafter methyl 4-[(E)-(2-methylphenyl)vinyl]benzoate (2.14 g) was obtained.

Methyl 4-[(E)-(2-methylphenyl)vinyl]benzoate

NMR ($CDCl_3$, δ): 2.44 (3H, s), 3.92 (3H, s), 7.01 (1H, d, J = 16.5 Hz), 7.18-7.25 (3H, m), 7.46 (1H, d, J = 16.5 Hz), 7.57 (2H, d, J = 8.5 Hz), 7.58 (1H, m), 8.03 (2H, d, J = 8.5 Hz).

(0110)

Production Example 13

Solution of methyl 6-(2,3-dimethylbenzoylamino)nicotinate (380 mg) obtained in Production Example 2 in a mixture of 1N sodium hydroxide aqueous solution (4 ml) and methanol (15 ml) was refluxed for one hour. Methanol was eliminated by distillation under reduced pressure, and remaining aqueous solution was adjusted to pH 4. The precipitated solid was recovered by filtration and dried, and 6-(2,3-dimethylbenzoylamino) nicotinic acid (343 mg) was obtained.

NMR ($CDCl_3$, δ): 2.24 (3H, s), 2.29 (3H, s), 3.32 (1H, br), 7.13-7.30 (3H, m), 8.27-8.33 (2H, m), 8.82 (2H, m).

(0111)

Production Example 14

Solution of methyl 4-[2-t-butoxycarbonyl-1-(2,3-dimethylbenzoyl)hydrazino]benzoate (561 mg) obtained in Production Example 4 in a mixture of 1N sodium hydroxide aqueous solution (5 ml) and methanol (10 ml) was refluxed for one hour, and methanol was eliminated by distillation under reduced pressure. The remaining aqueous solution was acidified with 1N hydrochloric acid, and the precipitated solid was recovered by filtration, and 4-[2-t-butoxycarbonyl-1-(2,3-dimethylbenzoyl)hydrazino]benzoic acid (361 mg) was obtained. This compound was used in the next step without further purification.

(0112)

Production Example 15

Using methyl 4-[(E)-(2-methylphenyl)vinyl]benzoate obtained in Production Example 12, 4-[(E)-(2-methylphenyl) vinyl] benzoic acid was obtained in the same way as in Production Example 14.

NMR (DMSO-d_6, δ): 2.41 (3H, s), 7.19 (1H, d, J = 16.5 Hz), 7.20-7.29 (3H, m), 7.58 (1H, d, J = 16.5 Hz), 7.70 (1H, m), 7.77 (2H, d, J = 8.5 Hz), 7.94 (2H, d, J = 8.5 Hz).

(0113)

Production Example 16

Solution of methyl 4-[2-acetyl-1-(2,3-dimethylbenzoyl)hydrazino]benzoate (600 mg) obtained in Production Example 6 in a mixture of 1N sodium hydroxide aqueous solution (4 ml) and methanol (15 ml) was stirred overnight at room temperature, and thereafter the mixture was stirred at 50° C for one hour. Methanol was eliminated by distillation under reduced pressure, and remaining aqueous solution was acidified with 1N hydrochloric acid. The precipitated solid was recovered by filtration and dissolved in chloroform. This solution was dried with magnesium sulfate, and the solvent was eliminated by distillation

under reduced pressure, and 4-[2-acetyl-1-(2,3-dimethylbenzoyl)hydrazino]benzoic acid (532 mg) was obtained.

NMR (DMSO-d_6, δ): 1.70 (1H, br), 2.20 (3H, s), 2.25 (3H, s), 3.34 (3H, s), 7.01-7.21 (3H, m), 7.37-7.65 (2H, m), 7.91 (2H, m).

(0114)

Production Example 17

To solution of 1-[2-(5-nitro) furoyl]-1,2,3,4-tetrahydroquinoline (1.00 g) obtained in Production Example 1 in a mixture of 30 ml methanol and dioxane (910 ml) was added 10 % palladium-charcoal (300 mg), and the mixture was hydrogenated for seven hours under 3 atmosphere. The catalyst was eliminated by filtration, and solvent was eliminated by distillation from the filtrate under reduced pressure, and 1-[2-(5-amino)furoyl]-1,2,3,4-tetrahydroquinoline (576 mg) was obtained as straw-coloured amorphous crystals. The crude product was used in the next step without further purification.

(0115)

Production Example 18

The following compounds were obtained in the same way as in Production Example 17.

1) 9-(4-aminobenzoyl)-5,6,7,8-tetrahydro-9H-pyrido[2,3-b]azepine

2) 5-(4-aminobenzoyl)-10,11-dihydro-5H-dibenzo[b,f]azepine

(0116)

Reference Example 1

To dichloromethane (20 ml) solution of 6-(2,3-dimethylbenzoylamino) nicotinic acid (343 mg) produced in Production Example 13 were added oxalyl chloride (0.176 ml) and several drops of N,N-dimethylformamide, and this solution was stirred at room temperature for two hours. The solvent was eliminated by distillation under reduced pressure, and corresponding acid chloride was obtained as yellow solid. This solid was added to 1,2,3,4-tetrahydroquinoline (203 mg) dissolved in pyridine (20 ml) and the mixture was stirred at room temperature for two hours. The solvent was eliminated by distillation under reduced pressure, and the residue was dissolved in 25 ml chloroform. This solution was washed with water and aqueous sodium chloride, and drying was carried out with magnesium sulfate. The solvent was eliminated by distillation under reduced pressure, and next the residue was purified by silica gel column chromatography (eluate; chloroform), and an oily substance was obtained. This oily substance was crystallised from the diethyl ether, and 1-[6-(2,3-dimethylbenzoylamino) nicotinoyl]-1,2,3,4-tetrahydroquinoline (244 mg) was obtained.

NMR ($CDCl_3$, δ): 2.07 (2H, tt, J = 6, 6 Hz), 2.31 (3H, s), 2.38 (3H, s), 2.84 (2H, t, J = 6 Hz), 3.93 (2H, t, J = 6 Hz), 6.66 (1H, d, J = 7.5 Hz), 6.93 (1H, dt, J = 1.5, 7.5 Hz), 7.05 (1H, dt, J = 1.5, 7.5 Hz), 7.12-7.34 (4H, m), 7.70 (1H, dd, J = 8.5, 2 Hz), 8.21 (1H, d, J = 2 Hz), 8.27 (1H, d, J = 8.5 Hz), 8.35 (1H, br s).

(0117)

Example 1

The following compounds were obtained in the same way as in Reference Example 1.

1) 4-[6-(2,3-dimethylbenzoylamino) nicotinoyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-b]azepine.

NMR ($CDCl_3$, δ): 1.81 (2H, m), 2.04 (2H, m), 2.33 (3H, s), 2.38 (3H, s), 2.94 (2H, m), 3.89 (2H, br), 6.28 (1H, d, J = 5 Hz), 6.79 (1H, d, J = 5 Hz), 7.17 (1H, dd, J = 7.5, 7.5 Hz), 7.29 (1H, d, J = 7.5 Hz), 7.40 (1H, d, J = 7.5 Hz), 7.75 (1H, d, J = 8.5 Hz), 8.15 (1H, s), 8.37 (1H, d, J = 8.5 Hz), 9.14 (1H, br).

(0118)

2) 1-{4-[2-t-butoxycarbonyl-1-(2,3-dimethylbenzoyl) hydrazino] benzoyl}-1,2,3,4-tetrahydroquinoline.

NMR ($CDCl_3$, δ): 1.45 (9H, s), 2.02 (2H, tt, J = 7, 7 Hz), 2.21 (3H, s), 2.24 (3H, s), 2.81 (2H, t, J = 7 Hz), 3.85 (2H, t, J = 7 Hz), 6.55 (1H, br), 6.75-7.31 (11H, m).

(0119)

3) 1-[4-[2-acetyl-1-(2,3-dimethylbenzoyl) hydrazino] benzoyl]-2,3,4,5-tetrahydro-1H-1-benzazepine.

NMR (DMSO-d_6, δ): 1.47 (1H, m), 1.60-2.20 (3H, m), 2.12 (6H, s), 2.20 (3H, s), 2.67 (1H, m), 2.81-3.12 (2H, m), 4.95 (1H, m), 6.70-7.30 (11H, m).

(0120)

4) 1-{4-[(E)-(2-methylphenyl) vinyl] benzoyl}-1,2,3,4-tetrahydroquinoline.

NMR ($CDCl_3$, δ): 2.06 (2H, tt, J = 6.5, 6.5 Hz), 2.40 (3H, s), 2.86 (2H, t, J = 6.5 Hz), 3.93 (2H, t, J = 6.5 Hz), 6.75 (1H, d, J = 7.5 Hz), 6.89 (1H, dt, J = 1.5, 7.5 Hz), 6.94 (1H, d, J = 16.5 Hz), 7.01 (1H, dt, J = 1.5, 7.5 Hz), 7.15-7.23 (4H, m), 7.31-7.43 (5H, m), 7.58 (1H, m).

(0121)

Example 2

Oxalyl chloride (0.139 ml) and one drop of N,N-dimethylformamide were added to dichloromethane (10 ml) solution of 1-(4-methylphenyl) pyrrole-2-carboxylic acid (202 mg) obtained in Production Example 11, and this solution was stirred at room temperature for two hours. The solvent was eliminated by distillation under reduced pressure, and the thereby obtained oily substance was added to dichloromethane (20 ml) solution of mixture of 1-(4-aminobenzoyl)-1,2,3,4-tetrahydroquinoline (253 mg) and triethylamine (0.21 ml). The mixture was stirred at room temperature for two hours, and the solution was washed sequentially with dilute hydrochloric acid, water and aqueous sodium chloride, and drying was carried out with magnesium sulfate. The solvent was eliminated by distillation under reduced pressure, and an oily substance was obtained. This crude oily substance was purified by silica gel column chromatography (eluate; 1 % methanol-containing chloroform), and 1-{4-[1-(4-methylphenyl) pyrrole-2-carbonyl] aminobenzoyl}-1,2,3,4-tetrahydroquinoline (308 mg) was obtained.

NMR ($CDCl_3$, δ): 2.02 (2H, tt, J = 7, 7 Hz), 2.40 (3H, s), 2.81 (2H, t, J = 7 Hz), 3.88 (2H, t, J = 7 Hz), 6.29 (1H, dd, J = 3, 4 Hz), 6.68 (1H, d, J = 7.5 Hz), 6.82-7.36 (13H, s) 7.58 (1H, s).

(0122)

Example 3

The following compounds were obtained in the same way as in Example 2.

1) 5-dimethylamino-1-{4-{[1-(4-methylphenyl) pyrrole]-2-carbonyl} aminobenzoyl}-2,3,4,5-tetrahydro-1H-benzazepine.

NMR ($CDCl_3$, δ): 1.30-3.05 (5H, m), 2.13 (3H, s), 2.42 (6H, s), 3.53 (1H, m), 4.04 (1H, m), 6.26 (1H, dd, J = 2.5, 4 Hz), 6.53-7.57 (15H, m).

(0123)

2) 1-[4-(2-cyano-3-phenyl cinnamoyl amino) benzoyl]-1,2,3,4-tetrahydroquinoline.

NMR ($CDCl_3$, δ): 2.04 (2H, tt, J = 7, 7 Hz), 2.83 (2H, t, J = 7 Hz), 3.87 (2H, t, J = 7 Hz), 6.66 (1H, d, J = 8 Hz), 6.87 (1H, dd, J = 8, 8 Hz), 7.00 (1H, dd, J = 8, 8 Hz), 7.08-7.58 (16H, m).

(0124)

3) 1-{4-[2-(3-phenylthiophene) carbonylamino] benzoyl}-1,2,3,4-tetrahydroquinoline.

NMR ($CDCl_3$, δ): 2.03 (2H, tt, J = 7, 7 Hz), 2.82 (2H, t, J = 7 Hz), 3.86 (2H, t, J = 7 Hz), 6.65 (1H, d, J = 8 Hz), 6.85 (1H, dd, J = 8.8 Hz), 6.92-7.19 (5H, m), 7.25 (2H, d, J = 8 Hz), 7.38 (1H, br s), 7.44-7.63 (6H, m).

(0125)

4) 1-[4-(2-phenyl nicotinoyl amino) benzoyl]-1,2,3,4-tetrahydroquinoline.

NMR ($CDCl_3$, δ): 2.04 (2H, tt, J = 7, 7 Hz), 2.83 (2H, t, J = 7 Hz), 3.87 (2H, t, J = 7 Hz), 6.66 (1H, d, J = 8 Hz), 6.86 (1H, dd, J = 8, 8 Hz), 6.94-7.33 (7H, m), 7.33-7.55 (4H, m), 7.56-7.80 (2H, m), 8.17 (1H, dd, J = 8, 2 Hz), 8.79 (1H, dd, J = 5, 2 Hz).

(0126)

5) 1-{4-[(5-methyl-3-phenylisoxazole-4-carbonyl) amino] benzoyl}-1,2,3,4-tetrahydroquinoline.

NMR ($CDCl_3$, δ): 2.03 (2H, tt, J = 7, 7 Hz), 2.80 (3H, s), 2.82 (2H, t, J = 7 Hz), 3.88 (2H, t, J = 7 Hz), 6.65 (1H, d, J = 8 Hz), 6.85 (1H, dd, J = 8, 8 Hz), 6.98 (1H, dd, J = 8, 8 Hz), 7.04-7.20 (4H, m), 7.26 (2H, d, J = 8 Hz), 7.51-7.72 (5H, m).

(0127)

Example 4

Oxalyl chloride (0.055 ml) and several drops of N,N-dimethylformamide were added to 2-(4-methylphenyl) benzoic acid (92.5 mg) dissolved in dichloromethane (5 ml), and this solution was stirred at room temperature for two hours. The solvent was eliminated by distillation under reduced pressure, and the thereby obtained oily substance was added to dichloromethane (20 ml) solution of mixture of 1-(6-amino) nicotinoyl-5-dimethylamino-2,3,4,5-tetrahydro-1H-benzazepine (123 mg) and triethylamine (0.07 ml). The mixture was stirred at room temperature for two hours, and the solution was washed with water and aqueous sodium chloride, and drying was carried out with magnesium sulfate. The solvent was eliminated by distillation under reduced pressure, and an oily substance was obtained. This crude oily substance was purified by silica gel column chromatography (eluate; 1 % methanol-containing chloroform) and 5-dimethylamino-1-{6-di [2-(4-methylphenyl) benzoyl] amino nicotinoyl}-2,3,4,5-tetrahydro-1H-benzazepine (103 mg) was obtained.

NMR ($CDCl_3$, δ): 1.30-2.95 (5H, m), 1.93 (3H, s), 2.34 (3H, s), 2.40 (6H, s), 4.03 (1H, m), 4.95 (1H, m), 6.4-8.2 (23H, m).

(0128)

Example 5

Solution of 1-{4-[2-t-butoxycarbonyl-1-(2,3-dimethylbenzoyl) hydrazino] benzoyl}-1,2,3,4-tetrahydroquinoline (95 mg) obtained in Example 1-2) in 80 % trifluoroacetic acid aqueous solution (5 ml) was stirred at room temperature for two hours. Ethyl acetate (10 ml) and saturated aqueous sodium bicarbonate solution (10 ml) were added to this

solution, and the organic layer was washed with aqueous sodium chloride, and drying was carried out with sodium sulfate. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (eluate; chloroform : methanol = 50 : 1). Product was solidified with diethyl ether, and 1-{4-[1-(2,3-dimethylbenzoyl) hydrazino] benzoyl}-1,2,3,4-tetrahydroquinoline (39.4 mg) was obtained.

NMR ($CDCl_3$, δ): 2.00 (2H, tt, J = 7, 7 Hz), 2.11 (3H, s), 2.20 (3H, s), 2.79 (2H, t, J = 7 Hz), 3.85 (2H, t, J = 7 Hz), 6.51 (1H, d, J = 8 Hz), 6.80 (1H, t, J = 8 Hz), 6.85-7.18 (9H, m).

(0129)

Example 6

To mixture wherein 1-{4-[1-(2,3-dimethylbenzoyl) hydrazino] benzoyl}-1,2,3,4-tetrahydroquinoline (150 mg) obtained in Example 5 and 37 % formaldehyde aqueous solution (36.5 mg) were added to mixture of methanol (5 ml) and ethyl acetate (0.2 ml), was added sodium cyanoborohydride (35.3 mg), and the mixture was stirred overnight at room temperature. This solution was diluted with 15 ml chloroform and was washed with sodium bicarbonate aqueous solution and aqueous sodium chloride. The separated organic layer was dried with sodium sulfate, and the solvent was eliminated by distillation under reduced pressure. The residue was purified by silica gel column chromatography (eluate; chloroform) and 1-{4-[1-(2,3-dimethylbenzoyl)-2-methylhydrazino] benzoyl}-1,2,3,4-tetrahydroquinoline (40.0 mg) was obtained.

NMR ($CDCl_3$, δ): 2.01 (2H, tt, J = 7, 7 Hz), 2.12 (3H, s), 2.29 (3H, s), 2.62 (3H, s), 2.79 (2H, t, J = 7 Hz), 3.85 (2H, t, J = 7 Hz), 6.09 (1H, br), 6.50 (1H, d, J = 8 Hz), 6.79 (1H, t, J = 8 Hz), 6.82-7.19 (9H, m).

(0130)

Example 7

The mixture wherein to pyridine (2 ml) were added 1-{4-[1-(2,3-dimethylbenzoyl) hydrazino] benzoyl}-1,2,3,4-tetrahydroquinoline obtained in Example 5 (150 mg) and benzenesulfonyl chloride (66.3 mg) was stirred at room temperature for two hours. Pyridine was eliminated by distillation under reduced pressure, and the residue was dissolved in chloroform. This solution was washed with dilute hydrochloric acid and aqueous sodium chloride, and drying was carried out with magnesium sulfate. The solvent was eliminated by distillation under reduced pressure, and the residue was solidified with diethyl ether, and 1-{4-[1-(2,3-dimethylbenzoyl)-2-phenylsulfonyl hydrazino] benzoyl}-1,2,3,4-tetrahydroquinoline (176 mg) was obtained.

NMR (DMSO-d_6, δ): 1.91 (2H, tt, J = 7, 7 Hz), 2.00 (3H, s), 2.17 (3H, s), 2.80 (2H, t, J = 7 Hz), 3.61 (2H, t, J = 7 Hz), 6.72 (1H, br), 6.80-7.20 (11H, m), 7.39-7.74 (5H, m).

(0131)

Example 8

1-{4-[1-(2,3-dimethylbenzoyl)-2-methylsulfonyl hydrazino] benzoyl}-1,2,3,4-tetrahydroquinoline was obtained in the same way as in Example 7.

NMR (DMSO-d_6, δ): 1.92 (2H, tt, J = 7, 7 Hz), 2.12 (3H, s), 2.18 (3H, s), 2.78 (2H, t, J = 7 Hz), 3.32 (3H, s), 3.70 (2H, t, J = 7 Hz), 6.55 (1H, d, J = 8 Hz), 6.78 (1H, t, J = 8 Hz), 6.92-7.24 (9H, m).

(0132)

Example 9

o-toluoyl chloride (223 mg) was added to dichloromethane (10 ml) solution of 4-(4-aminobenzoyl)-5,6,7,8-tetrahydro-4H-thieno[3,2-b]azepine (356 mg) obtained in Production Example 9, and thereafter, pyridine (207 mg) was added at 0° C. The reaction mixture was held at room temperature for one hour, and it was concentrated. The residue was diluted with ethyl acetate, and this solution was washed sequentially with water, 1N hydrochloric acid and aqueous sodium chloride, dried with magnesium sulfate and concentration was carried out. The residue was refined by crystallising from mixture of ethyl acetate and n-hexane, and 4-[4-(2-methylbenzoyl amino) benzoyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-b]azepine was obtained.

NMR ($CDCl_3$, δ): 1.68-1.89 (2H, m), 1.89-2.09 (2H, m), 2.48 (3H, s), 2.87-3.00 (2H, m), 3.66-4.07 (2H, br s), 6.23 (1H, br d, J = 3 Hz), 6.69 (1H, d, J = 6 Hz), 7.18-7.49 (5H, m), 7.49-7.61 (4H, m).

(0133)

Example 10

The following compounds were obtained in the same way as in Example 9.

1) 2,3-dimethyl-8-[4-(2-methylbenzoyl amino) benzoyl]-4,5,6,7-tetrahydro-8H-thieno[2,3-b]azepin-4-one.

NMR ($CDCl_3$, δ): 2.07-2.26 (2H, m), 2.19 (3H, s), 2.25 (3H, s), 2.50 (3H, s), 2.73-2.86 (2H, m), 3.97 (2H, t, J = 6 Hz), 7.19-7.70 (9H, m).

(0134)

2) 9-[4-(2-methylbenzoyl amino) benzoyl]-5,6,7,8-tetrahydro-9H-pyrido[2,3-b]azepine.

NMR (DMSO-d_6, δ): 1.54-1.97 (4H, m), 2.35 (3H, s), 2.84-3.06 (2H, br s), 7.12 (2H, d, J = 8 Hz), 7.10-7.21 (1H, m), 7.22-7.49 (4H, m), 7.57 (2H, d, J = 8 Hz), 7.79 (1H, dd, J = 2, 7 Hz), 8.01 (1H, dd, J = 2, 7 Hz).

(0135)

3) 5-[4-(2-methylbenzoyl amino) benzoyl]-10,11-dihydro-5H-dibenzo[b,f]azepine.
NMR ($CDCl_3$, δ): 2.48 (3H, s), 2.84-3.12 (2H, m), 3.50-3.75 (2H, m), 6.97-7.61 (17H, m).

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